UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/762,188 | 02/05/2001 | Tomokazu Nagano | 2520-0120P | 1286 |

2292 7590 04/03/2003

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

| EXAMINER |
|---|
| BUNNER, BRIDGET E |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 04/03/2003

8

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/762,188 | NAGANO ET AL. | |
| | Examiner | Art Unit | |
| | Bridget E. Bunner | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-15 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-26,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status of Application, Amendments and/or Claims*

The amendments of 05 February 2001 (Paper No. 4 and 25 April 2001 (Paper No. 5) have been entered in full. Claims 16-29 are added.

### *Election/Restrictions*

Applicant's election of Group II, claims 16-29, drawn to a method of treating or preventing ischemic disease or arterial disease comprising administering a composition comprising hepatocyte growth factor in Paper No. 7 (27 December 2002) is acknowledged. Applicant's election of the species of ischemic disease is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-15 and 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group and species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7 (27 December 2002).

Claims 16-26 and 28-29, as they read upon the species of ischemic disease, are under consideration in the instant application.

### *Specification*

1. The disclosure is objected to because of the following informalities:

2. The Brief Description of Drawings for Figure 5 at page 10, lines 9-10 of the specification does not indicate the difference between the black and white bars utilized in the Figure or what the numerical locations (1-5) represent.

3. The Brief Description of Drawings for Figure 7 at pg 10, lines 21-23 of the specification does not refer to Figures 7A-7C.

4. Regarding the Brief Description of Drawings for Figures 8 and 12, it cannot be determined what the difference is between these figures.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "A METHOD OF TREATING ISCHEMIC DISEASE BY INTRAMUSCULAR ADMINISTRATION OF HEPATOCYTE GROWTH FACTOR".

Appropriate correction is required.

***Claim Objections***

6. Claims 16 and 23 are objected to because of the following informalities:

Claims 16 and 23 recite a non-elected species.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 16-26 and 28-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hindlimb ischemia in a patient in need thereof, comprising: intramuscularly administering to a patient suffering from hindlimb ischemia an effective amount of a composition comprising hepatocyte growth factor (HGF), wherein the composition is transported to, distributed in, and acts on tissues that are local to the

region of administration, and wherein the composition has reduced transportation to, distribution in, and effect in blood or bodily organs other than those that are local to said region of administration, does not reasonably provide enablement for a method for treating or preventing ischemic disease in a patient in need thereof or a method for treating or preventing ischemic disease of the heart or extremities in a patient in need thereof, comprising administering to the patient at a region of administration, an effective amount of a composition comprising hepatocyte growth factor (HGF) as an active ingredient, wherein the composition is composition is transported to, distributed in, and acts on tissues that are local to or around said region of administration, and wherein the composition has reduced transportation to, distribution in, and effect in blood or bodily organs other than those that are local to said region of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims also recite that the composition is administered intramuscularly and said region of administration is a muscle. The claims also recite that the composition is administered subcutaneously, externally, or in the form of a cataplasm, and said region of administration is subcutaneous or intraepidermal. The claims recite the muscle is skeletal or cardiac. The claims recite that the composition is administered at a dose of 0.01 to 500 μg/kg or 0.1 to 10 μg/kg. The claims recite that the composition does not contain any substance that binds and adsorbs HGF.

The specification teaches that the rat and rabbits ASO models of hindlimb ischemia were produced and HGF or a vehicle was administered intramuscularly to the left femoral region (pg 28-33). The specification discloses that the I/N ratio (blood pressure in an ischemic limb/blood

pressure in a normal limb x 100) is significantly improved in the HGF administration groups, compared with the vehicle administration groups (pg 29, lines 11-13; pg 30, lines 24-27; pg 31-32; Figures 8-12). The specification also teaches that when HGF is administered intramuscularly, HGF concentrations in the liver and kidney are significantly low in comparison with intravenous administration. Also, when HGF is administered intramuscularly, the concentration is high in the muscle to which it is administered in comparison with intravenous administration (pg 18-20). However, the specification does not teach administration of HGF via any other method other than intramuscularly to treat ischemic disease and one skilled in the art would not be able to predict that other modes of administration of HGF would treat ischemic disease. For example, Pettit et al. (Trends Biotech 16: 343-349, 1998) teaches that considerable effort has been given to the transdermal delivery of pharmaceutical products, but clinical applications have been limited to non-protein drugs because of the skin's poor permeability to proteins and peptides (pg 343, ¶ 3). Additionally, the specification does not teach any methods or working examples that indicate all types of ischemia, such as cerebral, cardiac (i.e., heart), acute mesenteric, or renal ischemias, can be treated with HGF. As mentioned above, the specification only teaches that intramuscular administration of HGF treats hindlimb ischemia. Undue experimentation would be required of the skilled artisan to determine the best route of administration and dosage of HGF for each type of ischemia.

Furthermore, the specification does not disclose *preventing* any ischemic disease in any animal by administering a composition comprising HGF. The term "prevent" is interpreted as meaning that an activity will not occur, i.e. ischemic disease will not occur. Undue experimentation would be required of the skilled artisan to determine the quantity of HGF

administered, the best route of administration, the duration of treatment, and any possible side-effects to prevent all possible ischemic diseases.

Due to the large quantity of experimentation necessary to treat and prevent all types of ischemic diseases by administration of HGF via any route, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of HGF administered for treatment of all ischemias via all possible administration routes, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 16-26 and 28-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 16-26 and 28-29 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating that administration of HGF treats or prevents ischemic disease.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 16-25, and 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldberg et al. (U.S. Patent 6,498,144) in view of Pu et al. (J Surg Res 54(6): 575-583, 1993).

Goldberg et al. teaches contacting tissue with hepatocyte growth factor (HGF), also known as scatter factor (col 1, lines 33-34; col 8-11). Goldberg et al. teaches that the tissue may be fibrous, endothelial, epithelial, vesicular, cardiac, cerebrovascular, muscular, vascular, transplanted, or wounded (see claims; col 7, lines 6-10). Goldberg et al. discloses that the tissue is ischemic, including myocardial ischemic tissue, cerebrovascular ischemic tissue, and veno-occlusive diseased tissue (see claims; col 13-21). Goldberg et al. also discloses that HGF may be administered to a tissue or subject topically or by intravenous, intramuscular, intradermal, subcutaneous, or intraperitoneal injection in an amount of about 0.1-1000 ng/kg body weight (the bottom of col 4 through the top of col 5). It is noted that the above amount of HGF administered in Goldberg et al. overlaps with the dosages of HGF recited in claim 25 of the instant application. For example, 0.1 ng/kg is equal to 100 μg/kg.

Goldberg et al. does not teach that HGF is transported to, distributed in, and acts on tissue local to the region of administration. Goldberg et al. also does not teach that HGF has reduced transportation to, distribution in, and effect in blood or bodily organs other than those that are local to the region of administration.

Pu et al. discloses that growth factors administered locally rather than systemically have a more beneficial effect (pg 582, ¶ 2). Pu et al. teaches that the minimal systemic effect of growth factors *in vivo* when they are absorbed into the circulation may result from their short half-life and accumulation in some "filtering" organs in the body, such as the kidney and liver (pg 582, ¶ 2). Furthermore, Pu et al. teaches that pharmacological stimulators are most effective if delivered locally into ischemic tissues (Pu et al., pg 582, bottom of col 1).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administering HGF to ischemic tissues as taught by Goldberg et al. by utilizing a local administration technique as taught by Pu et al. The person of ordinary skill in the art would have been motivated to make that modification because the avoidance of unwanted systemic effects of angiogenic growth factors when administered *in vivo* in patients for treatment of ischemic problems may be crucial. The person of ordinary skill in the art reasonably would have expected success because methods of local administration were already being performed with other growth factors at the time the invention was made. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

***Conclusion***

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Goldberg et al. U.S. Patent 5,837,676

Kishino et al. U.S. Patent 6,472, 366

Kudo et al. U.S. Patent 6,436,388

Ferrara et al. U.S. Patent 6,133,231

Schaper et al. Circulation 95(11) : 2471-2472, 1997.

Morishita et al. Hypertension 33 : 1379-1384, 1999.

Baffour et al. J Vasc Surgery 16(2) : 181-191, 1992.

Takeshita et al. Circulation 90 : II-228-234, 1994.

Taniyama et al. Gene Therapy 8(3) : 181-189, 2001.

Pu et al. Eur J Vasc Endovasc Surg 9(2) : 189-196, 1995.

Uematsu et al. J Pharm Sci 88(1) : 131-135, 1999.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
March 31, 2003